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EFFECTS OF SOLVENTS ON THE TAUTOMERIZATION OF *N*,*N*-DIMETHYLGLYCINE

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The effects that solvents have on the tautomerization of *N*,*N*-dimethylglycine are analyzed and the solvent's dipolarity/polarizability and acidic properties appear to play important roles in the solvation of the zwitterionic tautomer. Owing to the existence of a stable intramolecular hydrogen-bonded conformer of the zwitterion, in which the acidic hydrogen of the ion is hydrogen bonded to the carboxylate functionality, solvation of the zwitterion by basic solvents is not very important. © 1997 John Wiley & Sons, Ltd.

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INTRODUCTION

For over a century, solvent effects on reaction rates and equilibria have been of concern to chemists.[1] For compounds that have acidic and basic functionalities, such as amino acids, the degree of ionization is usually dictated by medium effects. For example, the rate of gastrointestinal absorption of some ionizable drugs depends on the extent of ionization.[2] Analysis of solvent effects of the properties of compounds has been an area of interest to our research group.[3] In a previous paper,[4] we showed that in solution the population of the zwitterionic tautomer of *N*,*N*-dimethylvaline is dictated mainly by the acidic and basic properties of solvents. Evaluation of solvent effects on the properties of different compounds can be achieved from appropriate quantitative structure–property relationships (QSPR).[5] For the development of reliable QSPR, accurate property measurements are needed for a selected series of compounds. Owing to the limited solubility of most amino acids in a wide variety of solvents, accurate property determinations, including the tautomerization, are very difficult to achieve. For the limited number of amino acids that are soluble in polar solvents, such as water, the tautomeric equilibrium overwhelmingly favors the zwitterionic tautomer,[6] and subtle solvation effects on the tautomerization cannot be determined precisely.

Compared with unmethylated amino acids, *N*,*N*-alkylated amino acids are very soluble in a wide range of solvents[7] and, as a result, they represent a good model to study solvent effects on the properties of amino acids. In addition, *N*-alkylation of amino acids is known to increase the population of the neutral tautomer in solution;[8] thus, the tautomeric equilibrium of *N*-alkylated amino acids in solution is more sensitive to subtle solvation effects than that of unmethylated amino acids. In this paper, based on the zwitterionic distribution of *N*,*N*-dimethylglycine in different solvents, an analysis of the effects that solvents have on the tautomerization is carried out.

EXPERIMENTAL

The procedure used for the determination of the percentage of tautomeric zwitterion has been reported elsewhere.[9] Ambient temperature ^{1}H NMR spectra were recorded in deuterated solvents on an IBM (Bruker) NR/300 FT-NMR spectrometer.

RESULTS AND DISCUSSION

Table 1 shows the distribution of the zwitterionic tautomer of *N*,*N*-dimethylglycine (along with the predicted distribution) in different solvents. The experimental results in Table 1 indicate that the magnitude of the tautomeric equilibrium of *N*,*N*-dimethylglycine [equation (1)] is related to the nature of the solvent.

$$Me_2NCH_2COOH \rightleftharpoons Me_2NH^+CH_2COO^- \qquad (1)$$

Owing to the dipolar nature of the zwitterionic tautomer of amino acids, the tautomerization in solution is dictated

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Table 1. Solvatochromic parameters[a] and percentage of zwitterion of *N*,*N*-dimethylglycine in different solvents

Solvent	π^*	α	% Zwitterion	
			Experimental	Calculated[b]
(Gas phase)	−1·1	0·00	0[c]	2
Acetonitrile	0·76	0·15	66	65
Dimethyl sulfoxide	1·00	0·00	69[d]	69
Water	1·09	1·17	94	100
MeOH	0·60	0·98	86	79
Acetone	0·72	0·48	61	62
Dimethylformamide	0·88	0·69	67	66

[a] Ref. 10.
[b] Using equation (2).
[c] A. D. Headley and C. S. Giam, unpublished results.
[d] Ref. 9.

mainly by the solvation of the zwitterions.[11] In the absence of any solvent, i.e. the gas phase, it is known that amino acids exist as neutral tautomers.[12] Knowledge of the effects that solvents have on the different properties of compounds can be gained from linear solvation energy relationships (LSER).[13] Equation (2) shows the dual-parameter LSER obtained from the results in Table 1.

$$\%\ \text{zwitterion} = (32 \pm 3)\pi^* + (23 \pm 4)\alpha + 37 \pm 2 \qquad (2)$$

$$N=7;\ R=0{\cdot}993;\ SD=4{\cdot}5$$

For equation (2), the solvatochromic prameters π^* and α represent the solvents' dipolarity/polarizability and hydrogen bond acidity (HBA) properties, respectively.[10] Ideally, the use of more solvents with a wider range of solvent properties would have been preferred for the development of equation (2). Solvents, especially those which are less polar and more polarizable than those used would have been ideal. Owing to the low solubility, however, of the dimethylglycine salts used for the determination of the percentage of zwitterions, a wider range of solvents could not be utilized.

Nonetheless, based on the closeness of the regression coefficient (*R*) to unity for equation (2), the magnitude of the standard deviation (*SD*) and the ability of the equation to predict accurately the experimental results in Table 1, this equation can be used to gain some useful insight into the solvation effects on the tautomerization of *N*,*N*-dimethylglycine. The positive coefficients for the two solvation properties examined in equation (2) indicate that these solvation modes favor the solvation of the zwitterion. It was shown that for the solvation of the zwitterionic tautomer of *N*,*N*-dimethylvaline, the solvent properties that are important are the solvent's hydrogen bond acidity and basicity properties, and not the solvent's dipolarity/polarizability property.[4] For the solvation of the zwitterion of *N*,*N*-dimethylglycine, however, the solvent's dipolarity/polarizability appears to be an important factor, and the solvent's hydrogen bond basicity (HBD) was not found to be important. A three-parameter equation, in which π^* (solvent dipolarity/polarizability parameter), β (hydrogen bond basicity parameter) and α (hydrogen bond acidity parameter), which are non-colinear, are considered showed no improvement over equation (2), and the contribution from β was not statistically important.

One main difference between the zwitterions of *N*,*N*-dimethylvaline and that of *N*,*N*-dimethylglycine is that the former has a bulkier side-chain on the α-carbon and hence its zwitterion is more polarizable than *N*,*N*-dimethylglycine zwitterion. It is known that large polarizable ions are more stable than smaller less polarizable ions,[14] and hence smaller ions will be solvated to a greater extent than larger ions. The zwitterion of *N*,*N*-dimethylglycine is solvated to a greater extent, compared with the zwitterion of *N*,*N*-dimethylglycine (for the solvents used, the percentage of the zwitterion of dimethylglycine is greater than that of dimethylvaline). Also, the smaller size of the zwitterion of *N*,*N*-dimethylglycine, compared with that of *N*,*N*-dimethylvaline, allows the solvent molecules to interact more intimately with *N*,*N*-dimethylglycine zwitterion than *N*,*N*-dimethylvaline zwitterion, and hence the solvent dipolarity/polarizability is an important contributor to its solvation. For the solvation of *N*,*N*-dimethylglycine zwitterion, however, it may not be very obvious why the solvent 's HBA is important and the solvent's HBD is not. For the zwitterionic tautomer of glycine, one stable conformer is the intramolecular hydrogen bonded conformer.[15] Thus, the acidic hydrogen is not readily available to hydrogen bond to the solvent. For the larger *N*,*N*-dimethylvaline, the average tautomeric equilibrium favors the neutral tautomer,[2b] hence this intramolecular hydrogen-bonded zwitterionic conformer is not as important in solution. There is steric interaction between the isopropyl group on the α-carbon and the methyl group on the adjacent nitrogen. Figure 1 illustrates the intramolecular hydrogen-bonded conformer of *N*,*N*-dimethylglycine and its solvation by acidic solvents.

Also, it is known that the carboxylate functionality typically requires more than one solvent molecule for effective solvation,[16] compared with the dimethylammonium functionality, which typically hydrogen bonds to the basic site of only one solvent molecule.[17] Thus, if the acidic hydrogen of the dimethylglycine zwitterion is involved in

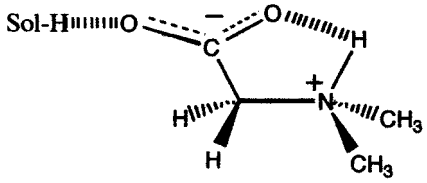

Figure 1. Solvation of the intramolecular hydrogen-bonded zwitterionic conformer of dimethylglycine

zwitterion by basic solvents is not as important as the other solvation modes.

In summary, the LSER developed from the solvatochromic parameters can be used to analyze solvent effects on the stability of the zwitterion of *N*,*N*-dimethylglycine. Even though the use of more solvents with a wider range of solvent properties would have been preferred for the development of the LSER, the relationship developed does give a fairly good indication of the nature of the solvation effects. Based on the relative magnitude of the coefficients of the LSER developed, solvent dipolarity/polarizability and acidity properties play important roles in the solvation of the zwitterion of *N*,*N*-dimethylglycine. Owing the the formation of a stable intramolecular hydrogen-bonded conformer, solvation of the zwitterion by a basic solvent is not important. The results of this study should reflect closely solvent effects on the tautomerization of other α-amino acids.

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